REMARKS

Pending Claims 2, 3, 8, 13, 14, 17-30, 34, 39, 44, 45, and 48-70 are under examination in this application.

Rejections Under 35 USC 103

In the Office Action, the Examiner rejected Claims 2, 3, 8, 13, 14, 17, 23, 23, 34, 44, 45, 48-49, 54, 62-63, and 68 as *prima facie* obvious over U.S. Patent No. 5,284,933 ("Affinity Peptides", hereinafter "Dobeli"). The Examiner also relies on Dobeli as the primary reference in combination with one or more other documents to reject claims under 35 USC 103. For the reasons provided below, Applicants respectfully traverse the rejections.

Dobeli describes and claims fusion proteins comprising a biologically active polypeptide or protein of interest linked by an amino and/or carboxy terminal "affinity peptide" comprising two to six consecutive histidine residues, which may be purified using a standard column of nickel chelating nitrilotriacetic acid-agarose resin particles (Ni-NTA) (see, e.g., Summary of the Invention, col. 1, line 35-col. 2, line 10; col. 8, line 25-col. 9., line 27; col. 25, line 55-col. 28, line 14; Claims 1-10, of Dobeli).

The Examiner stated that Dobeli:

> "teaches a method for isolating a fusion protein from a sample in a vessel (Abstract and Column 9, lines 8-19), comprising the steps of:
>
> a) combining the sample containing the fusion protein with metal-chelate affinity particles suitable for binding the protein, the affinity particles being insoluble in the sample (Column 9, lines 8-19);
>
> b) collecting the metal-chelate affinity particles (Column 9, lines 8-19);
>
> c) separating the remainder of the sample from the immobilized ***magnetic*** affinity particles (Column 9, lines 8-19, and Example 22);
>
> d) optionally, ***resuspending the affinity particles in a solution*** (Example 3, column 8, lines 20-23);

> e) optionally, eluting the fusion protein from the affinity particles, followed by separating the affinity particles from the eluted fusion protein (Column 9, lines 8-19);
>
> wherein any of the steps b), c), d), e) if present, and f) if present [sic] may optionally be also performed in the presence of the detergent, wherein the use of detergent is sufficient to reduce loss of particles during any separation step (Column 9, lines 8-19);
> . . ."
> (p. 3, the Office Action, emphasis added).

Applicants first note that Dobeli does not describe steps b, c, and d, as stated in the above excerpt from the Office Action. In particular, nowhere does Dobeli describe a step in a purification protocol as mentioned in step b of "collecting the metal-chelate affinity particles" ***after*** the step of binding of the fusion protein of interest to the affinity particles. Although Dobeli mentions that an NTA resin can be used batch-wise or in columns (col. 9, line 8, of Dobeli), the ***steps*** of every purification protocol described in Dobeli only employ affinity particles contained in columns, i.e., the affinity particles are never "collected" after binding fusion proteins of interest. Accordingly, Dobeli never describes a problem of losing affinity particles as can occur when the particles ***are*** manipulated during a purification process.

In addition, the affinity resin particles in Dobeli are ***not*** "magnetic affinity particles" as mentioned in step c in the above quotation from the Office Action. Dobeli provides ***no*** teaching or example of a purification process involving manipulations (e.g., collecting, resuspending) of magnetic affinity particles. Applicants only find that Example 22, cited by the Examiner, mentions that cells were extracted in a buffer using a magnetic stirrer (see, Example 22, col. 27, lines 6-9, of Dobeli) and that the resulting crude extract was pumped on to a column containing Ni-NTA affinity particles (see, Example 22, col. 27, lines 9-12, of Dobeli).

Furthermore, with respect to step d of the above quote from the Office Action, Applicants note that nowhere in Example 3, or anywhere else, does Dobeli actually describe purification of fusion proteins in which affinity particles are collected or resuspended. Again, Dobeli only describes steps in protocols for purifying fusion proteins using NTA affinity particles contained in columns. Accordingly, Dobeli provides no description of an optional or actual step in a purification process of "resuspending the affinity particles in a solution" after binding of the fusion protein to the affinity particles. Applicants further note that Example 3 of Dobeli only

describes construction of a recombinant vector, plasmid pGLS, encoding a fusion protein comprising IFN-γ.

In addition to the above technical mischaracterizations of the content of Dobeli, there is a clear and fundamental difference between Dobeli and Applicants' invention. Applicants' invention provides the means to enhance yields from a protein purification process using metal chelate affinity particles ***by reducing particle loss*** during manipulation of the particles by carrying out at least one step of the process in the presence of a detergent. Dobeli seeks to increase yields of proteins of interest using metal chelate affinity particles by making novel fusion proteins comprising various proteins of interest linked to one or more novel ***"affinity peptides"***. Dobeli teaches that linking a protein of interest with one or more such affinity peptides permits improved, indeed, "problem-free" protein purification:

> "This invention provides affinity peptides having at least two neighboring histidine residues which are especially suitable for the purification of recombinant proteins by means of metal chelate affinity chromatography in nitriloacetic acid (NTA) resins. ***These affinity peptides*** can be distinguished from the previously known peptides primarily in that they ***permit the problem-free purification of native and denatured proteins*** by means of NTA resins." (col. 1, lines 37-45, Summary of the Invention, of Dobeli, emphasis added)

Dobeli provides both a general formula and a nested set of several "especially preferred" species of such affinity peptides that may be used in making fusion proteins for purification by metal chelate affinity chromatography (see, e.g., col. 1, line 60-col. 2, line 10, of Dobeli). The purported benefit of fusion proteins comprising a protein of interest and such affinity peptides is reiterated in Dobeli following a description of an "especially preferred NTA resin":

> "An especially preferred NTA resin for the purification of the hybrid proteins of this invention has the formula:
>
> [FORMULA]
>
> "The NTA resin can be used batch-wise or in continuously operating columns to purify the fusion proteins, prior to loading with the fusion protein, the NTA resin is equilibrated with an aqueous buffer which itself does not form chelates with nickel, preferably a Tris·HCl buffer, pH 7.5. The equilibration buffer (and the elution buffer) can contain a denaturing agent or a detergent

> such as guanidine·HCl, urea or Triton. ***The addition of such a denaturing agent or detergent permits the problem-free operations even with fusion proteins which are poorly soluble in aqueous solution.***
>
> "The elution of the fusion proteins ***from the column*** can be carried out at a constant pH or with linear or discontinuously falling pH gradients. The optimal elution conditions depend on the amount and type of impurities which are present, the amount of material to be purified, the columns dimensions etc. and are easily determined by routine experimentation on a case-by-case basis." (col. 9, lines 1-27, Description of the Invention, of Dobeli, emphasis added).

With respect to the statement of adding a denaturing agent or detergent (highlighted above), both the plain English and the ***context*** of Dobeli (i.e., new affinity peptides) make clear that the addition of a denaturing agent or detergent is recommended for "problem-free" operations with fusion proteins that are "poorly soluble in aqueous solution". Thus, the teaching relates to overcoming solubility problems, and does ***not*** relate to reducing loss of affinity resin particles, as can occur when the particles are manipulated in a purification process. Moreover, the paragraph immediately following this statement regarding poorly soluble fusion proteins (see, above) as well as ***all*** of the examples of fusion protein purification (Examples 18-25) in Dobeli clearly indicate that the purification process ***cannot*** experience significant particle loss, not because of the presence of detergent, but because the particles are ***always contained in columns***. Clearly, both the disadvantage of losing affinity particles during manipulations and the advantage of Applicants' invention to reduce such particle loss are unrecognized and unappreciated by Dobeli. What Dobeli does not appreciate, Dobeli cannot teach or suggest to others.

The rejections, whether based in whole or in part (see, below) on Dobeli, appear to supplant Dobeli's own context with that of Applicants' disclosure, however, such a practice is strictly prohibited from a proper analysis for obviousness:

> "A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided ***only*** by the prior art references and the then-accepted wisdom in the field. *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one 'to fall victim to the insidious effect of a hindsight

> syndrome wherein that which ***only the invention taught is used against its teacher***.' *Id.* (quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983))." *In re Kotzab*, 217 F.3d 1365, 1369, 55 USPQ2d 1313, 1316 (Fed.Cir. 2000).

Casting the mind back ***prior to*** Applicants' invention, persons of ordinary skill in the art who read Dobeli were taught that the best way to improve yields of a protein of interest, is to make fusion proteins comprising the protein of interest linked to one or more of the affinity peptides of Dobeli, even if such fusion proteins are poorly soluble, and then to purify such fusion proteins using columns containing metal chelate affinity resins. Only Applicants' ***subsequent*** invention disclosure describes the problem of losing affinity particles during manipulations of the particles and how to reduce such loss using a detergent.

In view of the above explanation, Applicants respectfully submit that Dobeli clearly does not render Applicants' claims *prima facie* obvious under 35 USC 103(a). Accordingly, the Examiner is requested to reconsider and withdraw the rejections.

In the Office Action, the Examiner also rejected one or more claims as obvious over the primary reference Dobeli in combination with one or more additional documents, i.e., Dobeli and U.S. Patent No. 4,888,367 ("Quigley"); Dobeli and U.S. Patent No. 5,798,442 ("Gallant"); Dobeli and U.S. Patent No. 4,009,213 ("Stein"); Dobeli and U.S. Patent No. 5,284,933 ("Tsaur"); Dobeli and U.S. Patent No. 6,180,548 ("Taoda"); Dobeli and U.S. Patent No. 6,348,318 ("Valkirs"). Dobeli is relied on as the primary reference against Applicants' claimed invention as discussed above. The Examiner relies on each of Quigley, Gallant, Stein, Tsaur, and Taoda as a teaching of one or more species of a compound that may be employed in Applicants' invention, i.e., Quigley for polyoxyethylene sorbitol and SDS (sodium dodecyl sulfate); Gallant for CHAPS (3-[cholamindo-propyl)-dimehtyl-ammonio]-1-propanesulfonate); Stein for dodecyl trimethyl ammonium chloride; Tsaur for polyethylene polymer polyvinyl alcohol; and Taoda for titanium oxide. Valkirs is relied on as a teaching for applying a magnetic field to attract and immobilize magnetic, metal-chelate affinity particles. Applicants traverse the rejections for the reasons provided below.

Neither Dobeli nor any of the additional documents mentioned above provides any suggestion or motivation to be combined as presented by the Examiner to provide Applicants'

invention for reducing loss of metal-chelate affinity particles during manipulations of those particles using a detergent in the range of 0.0005% - 2%. Absent such a suggestion or motivation, the combinations are improper. There is no evidence of a motivation or teaching in Dobeli or any of these additional documents for these documents to be combined to serve as a basis for rejecting the claims. The patent law clearly forbids such unmotivated combinations of references as hindsight reconstruction, so that rejections based on such combinations are improper. *See, In re Kotzab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000).

Nevertheless, even if the documents are so combined, persons of ordinary skill in the art are still not provided with an appreciation of the problem of losing metal-chelate affinity particles during manipulations in affinity purification protocols or of Applicants' claimed invention to solve this problem. None of Quigley, Gallant, Stein, Tsaur, Taoda, or Valkirs, with or without Dobeli, describes the problem addressed and solved by Applicants' invention.

Quigley describes a process for neutralizing a slurry comprising a carboxyl-containing polymer in a solvent to yield a high polymer content thickening agent (see, e.g., col. 2, lines 3-27, of Quigley). One embodiment of the neutralization process may comprise at least one of a variety of surfactants having a "hydrophile-lipophile balance" ("HLB") greater than 10 (see, e.g., col. 8, line 27-col. 10, line 12, of Quigley). Nowhere does Quigley teach or suggest the problem of losing metal-chelate affinity particles when the particles are manipulated during a purification process or how to reduce such particle loss by carrying out at least one step of the purification process in the presence of 0.0005% - 2% (v/v) of a detergent. Accordingly, the combination of Quigley with Dobeli does not result in Applicants' claimed invention.

Gallant, Stein, Tsaur, and Taoda have previously been shown on this record as not teaching or suggesting how to reduce loss of metal-chelate affinity particles during manipulations of these particles. Although each of these documents describes use of a particular detergent or compound that may be employed in Applicants' invention, they each lack any description of the problem of losing metal-chelate affinity particles when such particles are manipulated or how to use a detergent to reduce such particle loss. Accordingly, like Quigley, none of these documents in combination with Dobeli makes Applicants' claimed invention obvious to persons of ordinary skill in the art.

Similarly, Valkirs cannot cure the deficiencies of Dobeli to render Applicants' claimed invention *prima facie* obvious. Valkirs describes a process for detecting or concentrating a "target analyte" of interest comprising the use of binding moieties (e.g., antibodies) that are specific for the target analyte and that are reversibly attached to the magnetic particles. After binding to target analytes, the magnetic beads are collected with a magnetic field and the binding moieties may be dissociated from the magnetic beads and/or from the captured target analytes as well (see, e.g., col. 12, lines 1-19; Figure 1; col. 21, line 49-col. 22, line 24; of Valkirs). Yet, nowhere does Valkirs describe the problem of losing metal-chelate affinity particles (which may be magnetic) during manipulation of such particles or Applicants' invention for reducing such particle loss. Accordingly, the combination of Dobeli and Valkirs fails to make Applicants' claimed invention obvious.

The inventive feature of Applicants' invention for reducing loss of metal-chelate affinity particles during manipulations of the particles does not reside in fusion proteins comprising known or new affinity sequence that preferentially bind metal-chelate affinity particles as in Dobeli; in known detergents as mentioned in Quigley, Gallant, Stein, Tsaur, and Taoda; in the use of known or new assemblies of binding molecules with magnetic beads as in Valkirs; or even in combination of such items. The combination of documents as presented in the Office Action provides no more than a collection of items that may be employed in Applicants' invention, but without any tangible teaching that would be necessary to carry out Applicants' claimed process. It is well established that merely collecting documents that describe or identify old elements that may be used in a claimed invention is not a proper basis for defeating patentability under 35 USC 103(a). *See, In re Kotzab*, 217 F.3d 1365, 1369-1370, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000). Accordingly, no combination of Dobeli and the other documents cited in the Office Action renders the claims *prima facie* obvious under 35 USC 103(a).

The above notwithstanding, Applicants also note that even if Dobeli, alone or in combination with any of the other cited documents, were viewed as providing an "accidental use" of Applicants' claimed invention for reducing particle loss, the law is clear that such accidental use is merely an unappreciated event, without profit to the art, and therefore without legal significance for anticipation or obviousness of an actual claimed invention. *See, e.g., In re Zierden*, 411 F.2d 1325, 1329, 162 USPQ 102, 105 (C.C.P.A. 1969) (*citing Pittsburgh Iron &*

Steel Foundries Co. v. Seaman-Sleeth Co., 248 F. 705 (3rd Cir. 1917)). Accordingly, the mere possibility that somehow one might unknowingly practice Applicants' invention is not a proper basis for rejecting Applicants' claims as obvious under 35 USC 103.

In view of all of the above, Applicants respectfully submit that none of the documents cited in the Office Action, alone or in combination, renders the claims obvious under 35 USC 103. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejections and to pass Claims 2, 3, 8, 13, 14, 17-30, 34, 39, 44, 45, and 48-70 to allowance.

Respectfully submitted,

Thomas R. Berka

Thomas R. Berka, Ph.D. (Reg. No. 39,606)
Leon R. Yankwich (Reg. No. 30,237)
Attorneys for Applicants
YANKWICH & ASSOCIATES
201 Broadway
Cambridge, Massachusetts 02139
telephone: (617) 374-3700
telecopier: (617) 374-0055

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

The undersigned hereby certifies that this correspondence and accompanying documents are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service under 37 CFR §1.10, postage prepaid, Express Mailing Label No. EV 325775169 US in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date indicated below.

October 6, 2003
Date

Stephanie L. Leicht
Stephanie L. Leicht